PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/000770	01.03.2005	01.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D519/00, C07D487/04, A61K31/55, A61P35/00

Applicant
SPIROGEN LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Authorized Officer

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 25

because:

☒ the said international application, or the said claims Nos. 25 with respect to industtrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000770

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☒ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7,10,12-17,26-32
	No:	Claims	8,9,11,18-25
Inventive step (IS)	Yes:	Claims	1-7,26-32
	No:	Claims	8-25
Industrial applicability (IA)	Yes:	Claims	1-24,26-32
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 25 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Art. 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

The arguments brought forward by the applicant are accepted. The non-unity objection is, by cosequence, withdrawn.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 00/12508 A (THE UNIVERSITY OF PORTSMOUTH HIGHER EDUCATION CORPORATION; THURSTON, D) 9 March 2000 (2000-03-09) cited in the application

D2: WO 00/12507 A (THE UNIVERSITY OF PORTSMOUTH HIGHER EDUCATION CORPORATION; THURSTON, D) 9 March 2000 (2000-03-09)

D3: Gregson et al.; J. Med. Chem. 47 (2004), 1161-1174

D4: Kamal et al.; Bioorg. Med. Chem. Lett. 13 (2003), 3955-3958

The present application discloses compounds of the general formulas Ia and Ib (claims 1-7), compounds of the general formulas IIIa and IIIb (claims 8-21), the compounds IIIa and IIIb for use in therapy (claim 22), pharmaceutical compositions thereof (claim 23), the usage thereof for the preparation of a medicament (claim 24), methods of treatment by administering the compounds IIIa or IIIb (claim 25), a method for synthesizing the compounds Ia or Ib (claims 26-28), and a method for synthesizing the compounds IIIa or IIIb (claims 29-32).

For the assessment of present claim 25 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The compounds IIIa consist of two pyrrolobenzodiazepine(PBD) moieties linked to each other in their respective 7-positions.

The compounds IIIb consist of two pyrrolobenzodiazepine(PBD) moieties linked to each other in their respective 8-positions.

Representatives of the compounds Ia, Ib and IIIa are not known in the art.

Numerous representatives of the compounds IIIb are known in the art, the following being only a selection of compounds which are representatives of the compounds IIIb as claimed

D1: Cpds. 79, 80, 89, 90, 217, 218
D2: Cpd. 34
D3: Cpds. 3a-3d, 4a-4b, 21a-21b
D4: Cpd. DSB-120

The subject-matter of claims 8-9,11,18-25 according to the present case is, by consequence, not novel in the sense of Article 33(2) PCT.

Discussion of inventive step

b. Intermediate compounds Ia and Ib

Closest prior art is any one of D1-D4.

It was demonstrated in the application that the special technical feature of two protecting groups in position 10 and 11 of the PBD system is suitable to simplify the hitherto

known synthetic route for the preparation of PBD dimers.

As intermediates having this special technical feature are nowhere suggested in the above-mentioned prior art documents, the compounds Ia and Ib cannot be considered obvious for the skilled man.

An inventive step in the sense of Article 33(3) can therefore be acknowledged for the subject-matter of claims 1-7 and, by consequence, 26-32.

b. Final products IIIa and IIIb

Closest prior art is D1.

This document - which was also acknowledged by the applicant in the description - exemplifies compounds consisting of two PBD moieties linked to each other in their respective 8-positions (i.e. representatives of the compounds IIIb, vide supra).

The problem of the present application was to provide further compounds consisting of two PBD moieties symmetrically linked with each other that are suitable as antitumor agents.

i. Compounds IIIb:

As representatives of these compounds are already known in the art, they have to be considered obvious by consequence.

ii. Compounds IIIa

This problem has been solved by representatives of the compounds IIIa, as was shown in the description.

The subject-matter of claims 8-25 does, however, not fulfil the requirements of Article 33(3) PCT due to the following reasons:

To be inventive a chemical compound should
a. possess a structure that is unexpected

b. exhibit a use or an effect which is unexpected (Guidelines C-IV, 9.10)
c. the compound has been prepared by an inventive process, but only in the case where a technical prejudice to its production or unsurmountable difficulties in its production were believed to exist (Guidelines C-IV, 9.8(d))

Requirement a. is not fulfilled in the present case, as dimeric molecules that are structurally exremely close to the compounds IIIb are disclosed in D1.

Requirement b. is not fulfilled, as the use of the compounds IIIa as anti-tumor agents cannot be considered unexpected in view of the teaching of D1 (unless it could be demonstrated by the applicant that the compounds IIIa can be distinguished from the compounds IIIb by an unexpected, i.e. surprising effect).

Requirement c. is not fulfilled:
The process for the preparation of the compounds IIIa is, due to the use of the inventive intermediates Ia and Ib, inventive (vide supra), however neither a technical prejudice nor insurmountable difficulties in their production have been overcome.

Furthermore the following is noted:

The Applicant is entitled to claim all obvious modifications of what was described (cf. Guidelines C-III, 6.2); alternative variations have to be supported by a certain number of examples (s. Guidelines C-II, 4.9); in this case the breadth of the main claim represents a reasonable generalisation of what has been exemplified, so that it can be assumed that every compound falling within its scope actually provides a solution to the problem underlying the invention.

Non-limiting terms like "optionally substituted" (this term not being followed by a list of specific substituents) as used in the product claims of the present application are, however, speculative in the sense of Article 33(3) PCT: They include a great variety of structural possibilities not yet explored by the applicant, the effect of which cannot be foreseen having regard to the problem underlying the present invention.

Non-limititing terms as cited above include
- chemical groups which are structurally so remote from those of the examples that the activity of molecules comprising them cannot be predicted within the limits of qualitative structure-activity-relationship considerations

- mutagenic and/or toxic groups
- known pharmacophoric groups with the same or a completely different activity which leads to hybrid molecules or bio-conjugates the actual biological activities of which are unpredictable,

i.e. it cannot be foreseen, whether those molecules provide a solution to the problem at all.

Further objections:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2-D4 is not mentioned in the description, nor are these documents identified therein.